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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,393	10/31/2003	Andras Gruber	E056 1071.1	3913

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,393	GRUBER ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *3,4,8-15,19-43 and 46-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,16-18,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *October 31, 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, on June 20, 2006 to the First Action on the Merits of this case mailed February 21, 2005, is acknowledged. Applicants continue to traverse the Restriction/Election requirement of October 24, 2005. In support of said traversal, Applicants provide the following arguments.

The polypeptides of SEQ ID NO: 1-4 are all thrombin variants, with only one or two amino acid variations from the wild-type. In addition, SEQ ID NO: 2 is part of SEQ ID NO: 1, while SEQ ID NO: 4 is part of SEQ ID NO: 3. Searching all sequences would not be a burden on the Office.

These arguments are not found, or are found, to be persuasive for the following reasons. As stated in the Restriction/Election requirement of October 24, 2005, SEQ ID NO: 1-4 are distinct inventions because said sequences are structurally and functionally distinct entities. In addition, the search for one of said sequences would not encompass the searches for all said sequences and searching all sequences would be a burden on the Office. Nonetheless, it is acknowledged that SEQ ID NO: 4 is encompassed by SEQ ID NO: 3. Therefore, restriction between SEQ ID NO: 3 and 4 is herein withdrawn.

Because Applicants did not present the above arguments in their original response to the Restriction/Election requirement of October 24, 2005, because Applicants have now requested withdrawal of the restriction between SEQ ID NO: 3 and 4, and because claims reciting SEQ ID NO: 4 are dependent from claims that recite SEQ ID NO: 3, any rejection herein of claims reciting SEQ ID NO: 4 will not be considered a new grounds of rejection.

Claims 1-58 are pending. It is acknowledged that Applicants have amended Claims 5, 6, and 44. Claims 3, 4, 8-15, 19-43, and 46-58 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Claims 1, 5-7, 16, 17, 44, and 45 are hereby reconsidered and Claims 2 and 18, reciting SEQ ID NO: 4, are herein considered.

Claim Set

It is noted that the status of Claims 13-15 as "original" is incorrect. The status of said claims is "withdrawn".

Specification-Objections

It is acknowledged that Applicants have amended the first sentence of the specification to claim priority to the parent application, US 10/165,442, now issued as US 6,706,512, as well as the provisional application US 60/297,089. However, the specification is objected to because said amendment stating "the disclosure of which is hereby incorporated herein in its entirety by reference" introduces New Matter to the specification.

Drawings

Figures 1-4 are objected to for being confusing. Neither said figures nor the legends thereto explain the labeling found in the figures. For example, in Figure 1: "16a", "36a", "16", "48", etc. Clarification is required.

Claims-Objections

Objection to Claim 44, for being dependent from a non-elected claim, is maintained.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

Rejection of Claims 1, 5-7, 16, 17, 44, and 45 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 5-7, 9, 10, 12, and 13 of US Patent 6,706,512, for the reasons previously stated, is maintained. Claims 2 and 18 are herein rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 2 and 11, respectively, of US Patent 6,706,512 for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 1, 5-7, and 16 under 35 U.S.C. 112, first paragraph, lack of enablement, for the reasons set forth in the prior action, is maintained. Claims 2 and 18 are herein rejected under 35 U.S.C. 112, first paragraph, lack of enablement, for the same reasons.

In support of their request that said rejection be withdrawn, Applicants argue the following. Thrombin has been well characterized. The specification provides guidance as to how to make and test all polypeptides having at least 80% homology to SEQ ID NO: 3 for the

desired activity. The skilled artisan would know how to make and test all said polypeptides. The scope of any polypeptide having at least 80% homology to SEQ ID NO: 3 is not unduly broad and it would not be undue experimentation to make and test all said polypeptides for the desired activity.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that the skilled artisan would know how to make and test all polypeptides having at least 80% homology to SEQ ID NO: 3 for the desired activity. However, determining which of all polypeptides having at least 80% homology to SEQ ID NO: 3 have the desired activity would require undue experimentation. Guo et al. teach, using a protein 3-methyladenine DNA glycosylase as a model, that the percentage of random single-substitution mutations that inactivate a protein is 34% and that this number is consistent with other studies in other proteins (pg 9206, parg 4). Guo et al. show that the percentage of active mutants for multiple mutations appears to be exponentially related to this percentage by the simple formula $(.66)^x \times 100\%$, where x is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 80% identity allows up to 59 mutations within the 295 amino acids of SEQ ID NO: 3 and, thus, only $(.66)^{59} \times 100\%$ or $2.2 \times 10^{-9}\%$ of random mutants having 80% identity would be active, i.e., 1 in 4.4×10^{10}. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants, despite even this being an enormous quantity of experimentation that would take a very long time to accomplish. But finding a few mutants within several billion or more, as in the claims to 80% identity, would not be possible. While enablement is not precluded by the necessity for routine screening, if a

large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Written Description

Rejection of Claims 1, 7, and 16 under 35 U.S.C. 112, first paragraph, insufficient written description, for the reasons set forth in the prior action, is maintained. Claims 2 and 18 are herein rejected under 35 U.S.C. 112, first paragraph, insufficient written description, for the same reasons.

In support of their request that said rejection be withdrawn, Applicants provide the following argument. The working examples of the specification are representative of the function of the claim thrombin variants. Further, the specification discloses making and testing thrombin variants.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that the specification discloses the activity of some thrombin variants as well as how to make and test thrombin variants for protein C activation and fibrinogen clotting activities. However, Claims 1, 7, and 16 fail to provide any functional limitations for the recited thrombin variants. Therefore, the polypeptides encompassed by the recited genus have any or no activity. The specification fails to describe said genus of polypeptides in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 1, 5-7, 16, 17, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gibbs et al, 1996 in view of Arosio et al, 2000 or Ayala et al, 2001, the reasons set forth in the prior action, is maintained. Claims 2 and 18 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Gibbs et al, 1996 in view of Arosio et al, 2000 or Ayala et al, 2001 for the same reasons.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) The claimed invention is directed to a thrombin variant having <u>two substitutions</u>, $W^{215}A$ and $E^{217}A$ (Applicants' emphasis). Each of Gibbs et al ($E^{217}A$) and Arosio et al ($W^{215}A$) teach only a single substitution.

(B) Neither Gibbs et al nor Arosio et al provides any suggestion or motivation for making a variant having two substitutions. In fact, Arosio et al teaches away from a double mutant in asserting that $W^{215}A$ thrombin is <u>the best</u> and is more potent than $E^{217}A$ thrombin (Applicants' emphasis).

(C) The claimed invention is non-obvious because of <u>unexpected properties</u> (Applicants' emphasis). The invention has provided a double mutant thrombin variant ($W^{215}A$ + $E^{217}A$) having a synergistic effect on reducing the release of fibrinopeptides (Tables 1 & 2).

(D) The Office asserts that suggestion and motivation to combine is based on the skilled artisan's desire to provide a thrombin variant with enhanced protein C activity and decreased fibrinogen cleavage. However, the combination of $W^{215}A$ and $E^{217}A$ produces a dramatically decreased, rather than enhanced, protein C activity.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: Neither Gibbs et al nor Arosio et al are required to disclose a thrombin variant having both $W^{215}A$ and $E^{217}A$ substitutions, since this a rejection under 35 U.S.C. 103(a), not under 35 U.S.C. 102.

(B) Reply: Arosio et al does not teach away from the recited invention. As acknowledged by Applicants, Arosio's statement is that "The differential effect on binding of fibrinogen and protein C makes the $W^{215}A$ mutant the best anti-coagulant thrombin reported to date" (Examiner's emphasis). Said statement does not teach away from looking for additional single or multiple mutations that produce a thrombin variant that has even better anti-coagulant activity. It is acknowledged that Arosio et al also state that, "the gain in anti-coagulant potency is larger [for the $W^{215}A$ mutant] than that of the $E^{217}A$ mutant" (pg 8098, parg 3). However again, said statement does not teach away from making a double $W^{215}A + E^{217}A$ mutant, or any other mutant. Moreover, Arosio et al teach that further studies are necessary to identify more precisely the epitopes for protein C binding and that the penultimate β-strand of thrombin's B chain, which includes residues 215-217, represents an important target for future mutagenesis studies (pg 8100, left column & pg 8101, parg 2). Also, see (C) below.

(C) Reply: It is acknowledged that, compared to each single mutation, double mutation of thrombin at $W^{215}A$ and $E^{217}A$ has a synergistic effect on reducing fibrinogen

cleavage. However, said synergistic effect is not unexpected. It was well known in the art that many enzymes have allosteric sites that act synergistically in both the activation and inhibition of the enzyme (Metzler et al, 2001). For example, Nikoshkov et al show that, compared to each single mutation, double mutation of steroid 21-hydroxylase at $P^{105}L$ and $P^{453}S$ has a synergistic inhibitory effect on enzyme activity (Fig 1). Thus, a synergistic effect of double mutation on the activity of an enzyme is not an unexpected or surprising result.

Moreover, Arosio et al suggest that residues W^{215} and E^{217} act allosterically. Specifically, they teach that perturbation of W^{215} propagates to the neighboring E^{217} residue, producing changes in the access to the S1 site and reduced Na^+ binding (pg 8100, right column). Said teachings of Arosio et al agree with Dang et al, 1995, wherein it is taught that thrombin is an allosteric enzyme, whose equilibrium between pro-coagulant and anti-coagulant activity is controlled by sodium (Fig 4). Thus, Applicants' assertion of unexpected results does not overcome the rejection of Claims 1, 2, 5-7, 16-18, 44, and 45 under 35 U.S.C. 103(a).

(D) Reply: It is acknowledged that the combination of $W^{215}A$ and $E^{217}A$ produces a dramatically decreased, rather than enhanced, protein C activity. Furthermore, each of $W^{215}A$ (Arosio et al; Table 1) and $E^{217}A$ (Gibbs et al; Table 1) produces some decrease in protein C activity. However, the skilled artisan would know that it is the ratio of protein C activity to fibrinogen clotting activity (PC/PF), not the absolute protein C activity, that determines whether the action of thrombin will be primarily anti-coagulation, via the activation of protein C, or pro-coagulation, via cleavage of thrombin (Arosio et al, pg 8095, parg 1). Compared to the activity of wild-type thrombin, each of the $W^{215}A$ and $E^{217}A$ mutations produces a variant having enhanced anti-coagulation activity, i.e. the PC/PF ratio is higher than for wild-type thrombin.

Thus, as disclosed by Arosio et al, wild-type PC/PF is 0.013, while $W^{215}A$ PC/PF is 2.2 (Table 1) and, as disclosed by Gibbs et al, wild-type PC/PF is 0.013, while $E^{217}A$ PC/PF is 0.24 (Arosio et al; Table 1). The skilled artisan would know that each mutation produces a thrombin variant having enhanced anti-coagulation activity.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
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PRIMARY EXAMINER